

## **REMARKS**

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the remarks and amendments herewith.

### **I. STATUS OF THE CLAIMS AND FORMAL MATTERS**

Claims 1, 4-12, 23-26, 28 and 29 are now pending, and claims 1-2, 4-12, 15-17, and 22-25 are under examination. Claims 1, 4-6, 23-26, 28 and 29 have been amended, and claims 2, 15-23, 27 and 30-32 have been cancelled, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

No new matter is added.

It is submitted that these claims are in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims and the remarks herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather the amendments and remarks are made simply to place the claims in better condition for examination and to correct typographical errors.

### **II. THE OBJECTIONS TO THE CLAIMS ARE OVERCOME**

Claims 1, 2 and 4-6 were objected to as containing misspellings.

Claims 15-17 were objected under 37 CFR 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claims 22 and 25 were objected to as containing misspellings.

Applicants respectfully submit that the amendments herein render the objections moot. Claims 15-17 have been cancelled, and the misspellings in the remaining claims have been corrected. Applicants remind the Examiner that English spellings are allowed by the MPEP in lieu of American spellings, however Applicants have made the requested correction to claim 25.

Accordingly, reconsideration and withdrawal of the objections to the claims is respectfully requested.

### **III. THE REJECTIONS UNDER 35 U.S.C. §112 ARE OVERCOME**

Claims 1, 4-12, 15-17 and 22-25 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as

to reasonably convey to one of skill in the art that the inventors had possession of the invention at the time of filing. Applicants respectfully traverse.

Specifically, the Office Action indicated the claims are drawn to a method of making a POI using any quaternary ammonium compound without providing in the specification distinguishing attributes shared by the members of the genus, structural features, or a correlation between the structure and requisite properties.

Initially, Applicants note that the specification provides working examples using several different quaternary ammonium compounds - namely;

CetylTrimehtyl Ammonium Chloride (CTAB) (see Examples 4, 6-13 and 15-19);

Benzalkonium chloride (BAC) (see Example 5);

Lauroyl Trimethyl Ammonium Bromide (LTAB) (see Examples 7 and 9);

Cetrimide(see Example 9);

Stearoyl Trimethyl Ammonium Bromide (STAB) (see Example 9);

Myristyl Trimethyl Ammonium Chloride (MTAC) (see Example 9);

Cetyl Trimethyl Ammonium Chloride (CTAC) (see Example 9); and

Stearoyl Trimethyl Ammonium Chloride (STAC) (see Example 9)

in methods to extract hexose oxidase according to revised claim 1.

Thus, Applicants respectfully submit that the description shows that *numerous and diverse* quaternary ammonium compounds can be used to extract hexose oxidase according to the method of the claims. Hence, the scope of the revised claims is commensurate with the contribution of the present invention to the art.

Although Applicants disagree with the statements of the Office Action, as indicated above, in order to advance prosecution, original claim 1 has been amended herein to incorporate the list of specifically quaternary ammonium compounds recited in original claim 2, which claim was not subject to this rejection.

Regarding claim 22, the Office Action asserted that the specification only teaches a single representative species of HOX (namely *Chondrus crispus* HOX). Applicants respectfully disagree.

Applicants respectfully direct the Examiner's attention to Example 1 of the present application, which teaches that the hexose oxidase (as shown in Figure 6) is not derived from *Chondrus Crispus* as such, but is actually derived from a synthetic gene designed to match the

preferred codon usage of different yeasts. In this regard, Applicants note that the skilled person would readily appreciate that certain species prefer to use specific codons (coding for specific amino acids). Thus, the alteration of a gene sequence to use the preferred codons of a specific species is within the routine repertoire of the skilled person.

Furthermore, no suggestion has been made that any member of the hexose oxidase family would behave any differently in an extraction process. Lacking evidence of any such differences, one of skill in the art would readily appreciate that any member of the hexose oxidase family could be extracted using the same process.

In fact, the Examples show that the method of present claim 1 can be used to derive completely different recombinant proteins of interest - namely recombinant IL-1ra and recombinant glucan lyases (see Examples 2-22 and Examples 25 and 29).

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 1, 2, 4-12, 15-17 and 22-25 were rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. Applicants respectfully traverse.

35 U.S.C. §112, first paragraph, requires that the specification describe how to make and use the invention. 35 U.S.C. §112, first paragraph, recites, in pertinent part:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same[.]

A patent claim is invalid if it is not, *inter alia*, supported by an enabling disclosure. The test for enablement requires a determination of whether any person skilled in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400, (Fed. Cir. 1988). The factors involved in determining whether there is sufficient evidence to support a finding of enablement include, among others, (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, and (8) the quantity of experimentation needed

to make or use the invention based on the content of the disclosure. *See Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404.

It is respectfully submitted that the present application satisfies the enablement requirements as described above.

Initially, the Office Action alleges that the specification does not reasonably provide enablement for a method of releasing a POI using any quaternary ammonium compound, although the Office Action does admit that the specification is enabled for those specific quaternary ammonium compounds described in previous claim 2.

As described above, Applicants note that the specification provides working examples using several different quaternary ammonium compounds. However, in the interest of advancing prosecution, Applicants have amended the claims herein to incorporate the specifically identified compounds of claim 2 into claim 1.

The Office Action also indicates that there is no guidance in the specification as to what the other essential conditions are for contacting the cell with a membrane extracting compound. Applicants respectfully disagree.

The skilled artisan, upon reading the application as a whole, would have readily realized that the conditions for contacting the cell with a membrane extracting compound are simply the regular culture conditions for culturing the host cell. See, for example, page 5, line 118, to page 6, line 127. In contrast to the assertions of the Office Action, the method does not require the skilled person to determine any special culture conditions for contacting the cells with the membrane extracting compound.

Furthermore, Applicants respectfully submit that the Examples show that the recombinant proteins can be obtained at a wide variety of temperatures (see Example 8). Indeed, the skilled artisan would have readily been able to determine the appropriate culture conditions for a particular host cell using techniques which are routine in the art, thereby precluding the need for “undue” experimentation as suggested by the Office Action.

Thus, Applicants respectfully submit that the pending claims are enabled, and that the scope of the claims is commensurate with that which is described in the specification and that which would be understood by a skilled artisan.

Accordingly, reconsideration and withdrawal of the enablement rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 24 and 25 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants respectfully traverse.

The Office Action states that original claim 24 is confusing for reciting “a nucleotide sequence set out in SEQ ID No 22”. Applicants respectfully submit that claim 24 has been amended to recite “the nucleotide sequence set out in SEQ ID No 22” in order to indicate that only one sequence is being referred to.

The Office Action further alleges that original claim 25 recites a complementary sequence that encodes HOX, but that a sequence which hybridizes to a coding strand does not, itself, code for the protein. Applicants respectfully submit that original claim 25 has been amended herein to remove reference to the sequence capable of hybridizing to SEQ ID No 22.

Thus, the rejections are now moot. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph, are respectfully requested.

### **III. THE ART REJECTIONS ARE OVERCOME**

Claims 1, 2, 4-12 and 15-17 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by, or in the alternative, under 35 U.S.C. §103(a) as obvious over Sekhar *et al.* The rejection is respectfully traversed.

Applicants respectfully remind the Examiner that a two-prong inquiry must be satisfied in order for a Section 102 rejection to stand. First, the prior art reference must contain all of the elements of the claimed invention, *see Lewmar Marine Inc. v. Barient Inc.*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987), and, the single prior art reference must contain an enabling disclosure, *see Chester v. Miller*, 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990).

Further, for a Section 103 rejection to be proper, there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings to arrive at the claimed invention. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, the Examiner is respectfully reminded that “obvious to try” is not the standard under 35 U.S.C. §103. *In re Fine*, 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): “The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the

prior art suggests the desirability of the modification.” Also, the Examiner is additionally respectfully reminded that for the Section 103 rejection to be proper, **both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants’ disclosure.** *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

The Examiner is also respectfully reminded that MPEP 2143.01 mandates that for a Section 103 rejection, there must be some suggestion or motivation to modify reference teachings, and, that MPEP 2143.02 further mandates that for a section 103 rejection, there must be a reasonable expectation of success.

Applicants respectfully assert that none of these requirements are met by Sekhar *et al.*

The Office Action alleges that Sekhar *et al.* teaches preparation of catalase and other enzymes from Bakers’ yeast cells permeabilized with CTAB; that in *S. cerevisiae*, catalase is an intracellular enzyme; that whole cells show very low catalase activity due to impermeability of the intact cell; and concentration, time, temperature and pH dependence of catalase activity in CTAB permeabilized yeast cells. The Office Action alleges that the claimed method is based on permeability of the cells, and that the POI is no consequence, such that it would be obvious to apply the method taught by Sekhar to release any POI from the yeast cells. Applicants respectfully disagree.

The present invention relates to methods of extracting a soluble or membrane associated intracellular recombinant protein of interest (POI) from a bacterial, yeast or fungal cell, the POI being released from the bacterial, yeast or fungal cell comprising **contacting the cell** with a membrane extracting composition comprising a **quaternary ammonium compound**, wherein the quaternary ammonium compound is selected from those identified in claim 1, and wherein the POI is hexose oxidase.

Sekhar *et al.* relate to the treatment of *Saccharomyces cerevisiae* cells with various treatments to alter the membrane permeability. One of the **eight** treatments mentioned in the document is the treatment of cells with CTAB and the enzyme which is monitored is catalase (Table 1). Furthermore, Sekhar *et al.* show that the activity of catalase in the cell-free extract is significantly lower than the catalase activity in the cell suspension itself (Figure 2).

Applicants note that Sekhar *et al.* does not teach or even suggest the expression of a recombinant protein in the cells or even isolating said recombinant protein from the cells. The Office Action’s assertion that it is not important whether a protein is recombinant or not is

incorrect, especially in view of the Office Action's Section 102 rejection. In order for a rejection to be proper, as indicated above, the cited reference must contain all of the recitations of the claim. That simply is not the case here. It is improper to discard the term "recombinant" from the claim for the purpose of making an art rejection.

Furthermore, under Section 103, the cited reference must provide motivation to modify the reference to arrive at the claimed invention of the recitations are not explicitly provided in the reference. Again, this is not true of the instant case. The present claims specify that the POI is hexose oxidase ("HOX"). Nowhere in Sekhar *et al* is the skilled artisan taught or even prompted to obtain the enzyme HOX over and above the plethora of other proteins which may potentially be expressed in a cell. To assert otherwise is *ex post facto* analysis.

Accordingly, as Sekhar *et al.* fails to teach each and every limitation of the claims, and fails to provide motivation to modify Sekhar *et al.* to arrive at the instant invention, the rejections based on Sekhar *et al.* are improper and must be withdrawn.

Claims 1, 2, 4-12, 15-17, 22, 23 and 25 were also rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Sekhar *et al.* in view of Hansen *et al.* The rejection is respectfully traversed.

The Office Action indicates that Hansen *et al.* teaches the purification of hexose oxidase from *Chondrus crispus*, and that it would have therefore been obvious to one of skill in the art to apply the method of Sekhur *et al.* to releast HOX. Applicants disagree.

Although Hansen *et al.* discloses the purification of hexose oxidase from *Chondrus crispus*, the method used by Hansen *et al.* for expressing and obtaining recombinant hexose oxidase from *P. pastoris* uses **mechanical disruption** by a French Press (last two paragraphs of page 11582). Moreover, Hansen *et al.* confirms that the protein obtained by this process has hexose oxidase activity (see Table III).

Hence, Hansen *et al* teach a suitable method for obtaining hexose oxidase. Thus, there is **no** motivation in Hansen *et al* to find another method by which to obtain hexose oxidase *let alone* a **non-mechanical** method such as one which uses a quaternary ammonium compound. To assert otherwise is *ex post facto* analysis.

Further, it is again noted that there must be some motivation to combine references for a Section 103 rejection to be proper. This is not the case. One of skill in the art would have no motivation to combine the teachings of Sekhar *et al.* and Hansen *et a.*. One of skill in the art

would simply not look to replace an effective mechanical method of disruption with a non-mechanical method. Nevertheless, even if the skilled artisan were to combine these documents - which is denied - then the skilled artisan would still not arrive at the present invention.

Consequently, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

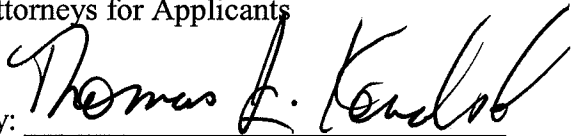
### **REQUEST FOR INTERVIEW**

If any issue remains as an impediment to allowance, prior to issuance of any paper other than a Notice of Allowance, an interview, is respectfully requested, with the Examiner, her supervisor, and, the Examiner is respectfully requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

### **CONCLUSION**

In view of the amendments, and remarks herein, the application is in condition for allowance. Reconsideration and withdrawal of the rejections of the application, and prompt issuance of a Notice of Allowance, is respectfully requested.

Respectfully submitted,  
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